SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pentacarinat 300mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

in terms of the active ingredient

Pentamidine Isetionate BP 300 mg (Equivalent to 172.4 mg pentamidine base)

3 PHARMACEUTICAL FORM

Sterile powder for use after reconstitution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pentamidine is indicated in the treatment of:

Pneumonia due to Pneumocystis carinii (PCP)
Leishmaniasis including visceral and cutaneous
Early phase African sleeping sickness caused by Trypanosoma gambiense.

All indications can be treated by deep intramuscular injection or intravenous injection.
Pneumocystis carinii pneumonia can also be treated by the inhalation route.

Pentacarinat is also indicated in the prevention of Pneumocystis carinii pneumonia in patients infected by the human immunodeficiency virus (HIV) who have experienced a previous episode of PCP. Administration is by the inhalation route.

4.2 Posology and method of administration

Pentamidine powder is reconstituted before use with Water for Injections BP. For intravenous use the required dose of pentamidine isetionate is diluted further in 50-250ml of glucose intravenous infusion BP or 0.9% (normal) Sodium Chloride Injection BP.

The following dosage regimens are recommended for adults, children and infants.

Treatment:
**Pneumocystis carinii pneumonia:**
By slow iv infusion, 4 mg/kg bodyweight of pentamidine isetionate once daily for at least 14 days.

If administered by inhalation, two 300 mg vials are dissolved in 6 ml of water for injection and the resultant solution administered by a suitable nebuliser once daily for three weeks.

**Leishmaniasis**
Visceral: 3-4 mg/kg bodyweight of pentamidine isetionate on alternate days to a maximum of 10 injections, preferably by im injection. A repeat course may be necessary.

Cutaneous: 3-4 mg/kg bodyweight, once or twice weekly by im injection until the condition resolves.

**Trypanosomiasis:**
4mg/kg bodyweight of pentamidine isetionate once daily or on alternate days to a total of 7-10 injections. The im or iv infusion route may be used.

There are no specific dosage recommendations for the elderly.

In renal failure the following recommendations are made for a creatinine clearance of less than 10ml/min.:

P. carinii pneumonia : in life threatening cases, 4 mg/kg bodyweight once daily for 7 to 10 days, then 4 mg/kg bodyweight on alternate days, to complete the course of at least 14 doses. In less severe cases, 4 mg/kg bodyweight on alternate days, to complete the course of at least 14 doses.

No dosage reductions are necessary in renally impaired patients with leishmaniasis or trypanosomiasis.

Hepatic failure : no specific dosage recommendations.

**Prevention**
Dissolve the contents of one pentacarinat vial (300 mg pentamidine isetionate) in 4-6 ml water for injections BP.

In the prophylaxis of P. carinii pneumonia, the adult dosage is 300 mg every 4 weeks or 150mg every 2 weeks.

### 4.3 Contraindications

The drug should not be administered to patients with a known hypersensitivity to pentamidine.

### 4.4 Special warnings and precautions for use

Pentamidine isetionate should be used with particular caution in patients with hepatic and/or renal dysfunction, hypertension or hypotension, hyperglycaemia or hypoglycaemia, leucopenia, thrombocytopenia or anaemia.
Fatalities due to severe hypotension, hypoglycaemia, acute pancreatitis and cardiac arrhythmias have been reported in patients treated with pentamidine isetionate, by both the intramuscular and intravenous routes. Baseline blood pressure should be established and patients should receive the drug lying down. Blood pressure should be closely monitored during administration and at regular intervals until treatment is concluded.

Therefore patients receiving pentamidine by inhalation should be closely monitored for the development of severe adverse reactions.

Pentamidine isetionate may prolong the QT interval. Cardiac arrhythmias indicative of QT prolongation, such as Torsades de Pointes, have been reported in isolated cases with administration of pentamidine isetionate. Therefore, pentamidine isetionate should be used with care in patients with coronary heart disease, a history of ventricular arrhythmias, uncorrected hypokalaemia and or hypomagnesaemia, bradycardia (<50 bpm), or during concomitant administration of pentamidine isetionate with QT prolonging agents.

Particular caution is necessary if the QTc exceeds 500 msec whilst receiving pentamidine isetionate therapy, continuous cardiac monitoring should be considered in this case. Should the QTc interval exceed 550 msec then an alternative regimen should be considered.

Laboratory monitoring: The following tests should be carried out before, during and after therapy by the parenteral route:

I) Blood urea, nitrogen and serum creatinine daily during therapy.
II) Complete blood and platelet counts daily during therapy.
III) Fasting blood glucose measurements daily during therapy, and at regular intervals after completion of therapy. Hyperglycaemia and diabetes mellitus, with or without preceding hypoglycaemia have occurred up to several months after cessation of therapy.
IV) Liver function tests (LFTs) including bilirubin, alkaline phosphatase, aspartate aminotransferase (AST/GOT), and alkaline aminotransferase (ALT/GPT). If baseline measurements are normal and remain so during therapy, test weekly. When there is baseline elevation in LFTs and/or LFTs increase during therapy, continue monitoring weekly unless the patient is on other hepatotoxic agents, when monitoring every 3-5 days is appropriate.
V) Serum calcium, test weekly. Serum magnesium, test twice weekly.
VI) Electrocardiograms at regular intervals.
VII) Urine analysis and serum electrolytes daily during therapy.

The benefit of aerosolised pentamidine therapy in patients at high risk of a pneumothorax should be weighed against the clinical consequences of such a manifestation.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is advised when pentamidine isetionate is concomitantly used with drugs that are known to prolong the QT interval such as phenothiazines, tricyclic antidepressants, terfenadine and astemizole, IV erythromycin, halofantrine and quinolone antibiotics (see Warnings section).
4.6 Pregnancy and lactation

There is no evidence of the safety of pentamidine isetionate in human pregnancy. A miscarriage within the first trimester of pregnancy has been reported following aerosolised prophylactic administration. Pentamidine isetionate should not be administered to pregnant patients unless considered essential.

Lactation: The use of pentamidine isetionate is contra-indicated in breast feeding mothers unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

Pentamidine has no known effect on the ability to drive and use machines.

4.8 Undesirable effects

Pentamidine isetionate may prolong the QT interval. Isolated cases of Torsades de Pointes have been reported with the administration of pentamidine isetionate.

Parenteral Route
Severe reactions which may be life threatening include hypotension, hypoglycaemia, pancreatitis, cardiac arrhythmias, leucopenia, thrombocytopenia, acute renal failure, hypocalcaemia. A possible case of Stevens-Johnson syndrome has been reported.

Less severe reactions include azotemia, abnormal liver function tests, leucopenia, anaemia, thrombocytopenia, macroscopic haematuria, hypomagnesaemia, hyperkalaemia, nausea and vomiting, hypotension, dizziness, syncope, flushing, hypoglycaemia, hyperglycaemia, rash, taste disturbances.

Rhabdomyolysis has been rarely reported following intramuscular administration of pentamidine isetionate.

Local reactions can occur ranging in severity from discomfort and pain to induration, abscess formation and muscle necrosis.

Reversible renal side effects occur with the highest frequency (over 20% of patients) with a slightly lower frequency of local reactions.

Side effects including metabolic disturbances, hepatic, haematological, or hypotensive episodes occur much less frequently (5-10% patients).

Inhalation Route:

Bronchospasm has been reported to occur following use of the nebuliser. This has been particularly noted in patients who have a history of smoking or asthma. This can usually be controlled by prior use of bronchodilators.

The occurrence of cases of pneumothorax has been reported in patients presenting a history of PCP. Although the aetiology of the pneumothorax was not linked primarily to the aerosolised
administration of pentamidine in the majority of cases, a causal relationship to pentamidine cannot be ruled out.

Local reactions involving the upper respiratory tract can occur ranging in severity from cough, shortness of breath and wheezing, bronchospasms to eosinophilic pneumonia.

Other side effects reported were hypotension, hypoglycaemia, acute pancreatitis, renal insufficiency rash, fever, decrease in appetite, taste disturbances, fatigue, light-headedness and nausea.

4.9 Overdose

Treatment is symptomatic. Cardiac rhythm disorders, including Torsades de Pointes, have been reported following overdose of pentamidine isetionate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pentamidine isetionate is an aromatic diamine. It is an antiprotozoal agent which acts by interfering with DNA and folate transformation, and by the inhibition of RNA and protein synthesis.

5.2 Pharmacokinetic properties

After intravenous infusion, plasma levels of pentamidine fall rapidly during the first two hours to one twentieth of peak levels, followed by a much slower decline thereafter. After intramuscular administration, the apparent volume of distribution of pentamidine is significantly greater (>3 times) than that observed following intravenous administration.

Elimination of half-lives after parenteral administration were estimated to be about 6 hours after intravenous infusion in patients with a normal renal function. The elimination of half-life following intramuscular injection was found to be about 9 hours.

Following parenteral administration, pentamidine appears to be widely distributed in the body and probably accumulates in tissue, particularly the liver and kidney. Only a small amount is excreted unchanged in the urine.

When administered by the use of a nebuliser, human kinetic studies revealed significant differences when compared to parenteral administration. Aerosol administration resulted in a 10-fold increase in bronchial alveolar lavage (BAL) supernatant fluid and an 80-fold increase in BAL sediment concentrations in comparison with those seen with equivalent intravenous doses.

Limited data suggests that the half-life of pentamidine in BAL fluid is greater than 10 to 14 days. Peak plasma concentrations after inhalation therapy were found to be approximately 10% of those observed with equivalent intramuscular doses and less than 5% of those observed
following intravenous administration. This suggests that systemic effects by the inhalation route are less likely.

Long term pulmonary parenchymal effects of aerosolised pentamidine are not known. Lung volume and alveolar capillary diffusion, however, have not been shown to be affected by high doses of pentamidine administered by inhalation to AIDS patients.

5.3 Preclinical safety data

No additional data of relevance to the prescriber

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable

6.2 Incompatibilities

Pentamidine isetionate solution should not be mixed with any injection solutions other than Water for Injections BP, Glucose Intravenous Infusion BP and 0.9% (normal) Sodium Chloride Injection BP.

6.3 Shelf life

60 months when unopened. After reconstitution 24 hours.

6.4 Special precautions for storage

Store the dry product below 30°C. Store the reconstituted product (for intravenous infusion) at 2-8°C. Use within 24 hours.

6.5 Nature and contents of container

Cardboard carton containing 5 x 10 ml glass vials each with rubber bung and aluminium ring. Each vial contains 300 mg Pentamidine Isetionate BP.

6.6 Special precautions for disposal
This product should be reconstituted in a fume cupboard. Store the dry product below 30°C. Store dilute reconstituted drug solutions between 2-8°C, and discard all unused portions within 24 hours of preparation. Concentrated solutions for administration by the inhalation or intramuscular routes should be used immediately.

After reconstitution with Water for Injections BP, pentacarinat should not be mixed with any injection solutions other than Glucose Intravenous Infusion 5% BP and 0.9% (normal) Sodium Chloride Injection BP.

The optimal particle size for alveolar deposition is between 1 and 2 microns.

The freshly prepared solution should be administered by inhalation using a suitable nebuliser such as a Respirgard II (trade mark of Marquest Medical Products Inc.), Modified Acorn system 22 (trade mark of Medic-Aid) or an equivalent device with either a compressor or piped oxygen at a flow rate of 6 to 10 Litres/Minute.

The nebuliser should be used in a vacated, well ventilated room. Only staff wearing adequate protective clothing (mask, goggles, gloves) should be in the room when nebulisers are being used.

A suitable well fitted one-way system should be employed such that the nebuliser stores the aerosolised drug during exhalations and disperses exhaled pentamidine into a reservoir. A filter should be fitted to the exhaust line to reduce atmospheric pollution. It is advisable to use a suitable exhaust tube which vents directly through a window to the external atmosphere. Care should be taken to ensure that passers-by will not be exposed to the exhaust.

All bystanders including medical personnel, women of child bearing potential, pregnant women, children, and people with a history of asthma, should avoid exposure to atmospheric pentamidine resulting from nebuliser usage.

Dosage equivalence: 4 mg of pentamidine isetionate contains 2.3 mg pentamidine base; 1 mg of pentamidine base is equivalent to 1.74 mg pentamidine isetionate. Displacement value: 300 mg of pentamidine isetionate displace approximately 0.15 ml of water.

MARKETING AUTHORISATION HOLDER

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7
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9\textsuperscript{th} January 2007

Legal Category

POM